Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
October 17, 2011

Location: FDA White Oak Campus, Building 31, Great Room (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Avenue Silver Spring, Maryland

Issue: The committee discussed supplemental new drug application (sNDA) 21641 (013) for AZILECT (rasagiline mesylate) Tablets, manufactured by Teva Neuroscience, Inc., for the following proposed indication: Treatment of patients with idiopathic (of unknown cause) Parkinson's disease to slow clinical progression and treat the signs and symptoms of Parkinson's disease as initial monotherapy (the single drug used to treat) and as adjunct (additional) therapy to levodopa.

These summary minutes for October 17, 2011 Peripheral and Central Nervous System Drugs Advisory Committee Meeting were approved on November 14, 2011.

I certify that I attended the October 17, 2011, Peripheral and Central Nervous System Drugs Advisory Committee Meeting and that these minutes accurately reflect what transpired.

/s/
Philip Bautista, Pharm.D.
Acting Designated Federal Officer, PCNS

/s/
Nathan Fountain, M.D.
Acting Chair, PCNS

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
October 17, 2011

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on October 17, 2011. A verbatim transcript will be available in approximately four weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm235850.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 17, 2011 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503) White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Teva Neuroscience, Inc. The meeting was called to order by Nathan Fountain, M.D. (Acting Chair); the conflict of interest statement was read into the record by Philip Bautista, Pharm.D. (Acting Designated Federal Officer). There were approximately 100 persons in attendance. There were seven (7) Open Public Hearing speakers.

Issues: The committee discussed supplemental new drug application (sNDA) 21641 (013) for AZILECT (rasagiline mesylate) Tablets, manufactured by Teva Neuroscience, Inc., for the following proposed indication: treatment of patients with idiopathic (of unknown cause) Parkinson's disease to slow clinical progression and treat the signs and symptoms of Parkinson's disease as initial monotherapy (the single drug used to treat) and as adjunct (additional) therapy to levodopa.

Attendance:
PCNS Members (Voting): Nathan B. Fountain, M.D. (Acting Chair); Samuel A. Frank, M.D. (Consumer Representative); Pooja Khatri, M.D., FAHA; Ellen J. Marder, M.D.; Jason W. Todd, M.D.

PCNS Members (Voting) Not Present: Jeffrey A. Cohen, M.D.; Dean D. Kindler, M.D.

Temporary Voting Members: J. Eric Ahlskog, M.D, Ph.D.; Kevin Black, M.D.; Jacqueline Christensen (Patient Representative); Robert R. Clancy, M.D.; Ralph B. D'Agostino, Ph.D.; Susan S. Ellenberg, Ph.D.; Thomas R. Fleming, Ph.D.; Vanessa Hinson, M.D., Ph.D.; Robert L. Rodnitzky, M.D.; Paul B. Rosenberg, M.D.; Hongyu Zhao, Ph.D.; Justin A. Zivin, M.D., Ph.D.

PCNS Members (Non-Voting): Roy E. Twyman, M.D. (Industry Representative)

FDA Participants (**Non-Voting):** Ellis Unger, M.D.; Russell Katz, M.D.; Gerald Podskalny, D.O.; Tristan Massie, Ph.D.

Acting Designated Federal Officer (Non-Voting): Philip Bautista, Pharm.D.

Open Public Hearing Speakers: Amy Comstock Rick (Parkinson's Action Network); Joyce Oberdorf (National Parkinson Foundation); Fernando L. Pagan, M.D. (National Parkinson Foundation); Stuart Isaacson, M.D.; James William Langston, M.D. (Parkinson's Institute and Clinical Center); John M. Baumann, B.B.A, J.D.; Laxman Bahroo, D.O.

The agenda proceeded as follows:

7:30 a.m.	Call to Order and Introduction of Committee	**Nathan Fountain, M.D.** Acting Chair, PCNS
7:40 a.m.	Conflict of Interest Statement	**Philip Bautista, Pharm.D.** Acting Designated Federal Officer, PCNS
7:45 a.m.	FDA Introductory Remarks	**Russell Katz, M.D.** Director Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
8:00 a.m.	**SPONSOR PRESENTATION**	**Teva Neuroscience, Inc.**
	Introduction	**Dennis Ahern, M.S.** Senior Director Regulatory Affairs Teva Neuroscience, Inc.
	Discussion of Medical Need	**C. Warren Olanow, M.D.** Mount Sinai School of Medicine
	TEMPO & ADAGIO Trials	**Cheryl Fitzer-Attas, Ph.D.** Director of Scientific and Medical Affairs Teva Neuroscience, Inc.
	Interpreting the Rasagiline Delayed-start Studies	**C. Warren Olanow, M.D.** Mount Sinai School of Medicine
	Conclusion	**Cheryl Fitzer-Attas, Ph.D.** Director of Scientific and Medical Affairs Teva Neuroscience, Inc.
9:30 a.m.	Clarifying Questions	
9:45 a.m.	**BREAK**	

10:00 a.m.	**FDA PRESENTATION**	
	sNDA 21641 (013): Rasagiline Delayed Start Trials in Parkinson's Disease	**Tristan Massie, Ph.D.** Mathematical Statistician Division of Biostatistics I (DB-I) Office of Biostatistics (OB) Office of Translational Science (OTS) CDER, FDA
11:15 a.m.	Clarifying Questions	
11:30 a.m.	**LUNCH**	
12:30 p.m.	Open Public Hearing Session	
1:30 p.m.	Questions to the Committee/Committee Discussion	
3:00 p.m.	**BREAK**	
3:15 p.m.	Questions to the Committee/Committee Discussion	
5:00 p.m.	**ADJOURNMENT**	

Questions to the Committee:

1. **Discussion:** Please discuss whether the randomized start design, appropriately designed and conducted, is capable of detecting a disease modifying effect for treatment of patients with Parkinson's disease? If not, are there alternative designs that can demonstrate such an effect?

   Committee Discussion*: The majority of the committee agreed that the randomized start trial design is capable of detecting a disease modifying effect with some members dissenting, but all members agreed that its interpretation can be complicated by the numerous factors discussed below.*

2. **Discussion:** (Agency reviewers have identified numerous issues related to the analyses/results of ADAGIO (**A**ttenuation of **D**isease Progression with **AGI**LECT®/AZILECT® **O**nce Daily) and TEMPO (**T**VP-1012 in **E**arly **M**onotherapy for **P**arkinson's Disease **O**utpatients), including:
   - **a.** Non-linearity of slopes, presumably related to varying early effects of treatment
   - **b.** Re-analyses of slopes without early data suggest parallel slopes in Phase 1 for drug and placebo
   - **c.** Potentially significant baseline differences in UPDRS (Unified Parkinson's Disease Rating Scale) scores between ES (early start) and DS (delayed start) patients in the Hypothesis 2 & 3 datasets, and potential biases in the analyses that compare these non-randomized groups
   - **d.** Differential response in men and women (primarily in ADAGIO), and baseline differences in early and delayed women starters in ADAGIO
   - **e.** Sponsor-conducted analyses that differed from those specified in the protocol

Please discuss the impact these issues, as well as any other issues you consider important, have on your interpretation of the studies submitted.

Committee Discussion:
2a. The Committee agreed that the pharmacodynamics of rasagiline are not fully understood as patients have different responses and they will not all achieve maximum symptomatic benefit at the same time. They noted that these different responses might account for the interpretation of non-linearity of slopes in the early phase of the study.

2b. The Committee agreed that more data points may have been helpful in defining the linearity of the slopes in the first phase of the study and knowing when a patient achieves maximum symptomatic benefit from treatment would better help define a relationship (whether it is linear or not) between treatment and the UPDRS scores. The Committee noted that the re-analysis of slopes without early data leaves little information to rely upon to form conclusions.

2c. The Committee noted that potentially significant baseline differences in the UPDRS scores going into the second phase may prevent the results from being considered compelling. Committee members suggested that potential biases may lie in the possibility of unblinding of treatment assignment in the first phase by patients once they started rasagiline in the second phase of the study.

2d. The Committee did not voice a definitive opinion regarding the differential response in men and women in the 1 mg group in the ADAGIO trial.. The observation should be considered hypothesis generating and additional information is needed to conclude there are different effects of rasagiline based on gender.

2e. The Committee believes that the Sponsor's analyses were reasonable and important to take into consideration. However, the primary analyses did not yield robust, statistically significant results. Many of the supportive analyses were performed post-hoc and they were associated with a small effect size. Please see the transcript for details of the Committee discussion.

3. **Vote:** Does ADAGIO provide compelling evidence that the 1 mg dose of rasagiline met the protocol specified criteria for success?

Vote: ***Yes= 0*** ***No = 17*** ***Abstain = 0***

Committee Discussion: *The Committee voted unanimously that ADAGIO did not provide compelling evidence that the 1 mg dose of rasagiline met the protocol specified criteria for success. The Committee noted that there may have been a signal of some activity in the 1 mg group; however, because the trial did not meet the required criteria specified by protocol, the evidence was not compelling. Some members expressed concern that the signal was a result of a symptomatic effect rather than a disease modifying effect. Please see the transcript for details of the Committee discussion.*

4. **Vote:** The 2 mg dose failed to show a differential effect between the early and delayed starters at the end of the study. The sponsor has offered some explanations (e.g., patients in the worst quartile of baseline UPDRS scores seemed to have a better response than other patients). Did the 2 mg group fail to meet the protocol specified criteria for success?

   Vote: ***Yes=17*** ***No = 0*** ***Abstain = 0***

   Committee Discussion: *The Committee unanimously voted that the 2 mg group failed to meet the protocol specified criteria for success. Please see the transcript for details of the Committee discussion.*

5. **Vote:** Has the sponsor provided substantial evidence of effectiveness for rasagiline as a treatment to delay clinical disease progression in patients with Parkinson's disease?

   Vote: ***Yes=0*** ***No = 17*** ***Abstain = 0***

   Committee Discussion: *The Committee unanimously voted that the sponsor did not provide substantial evidence of effectiveness for rasagiline as a treatment to delay clinical progression in patients with Parkinson's disease. The Committee agreed that there is currently an unmet need for disease modifying treatments in patients with Parkinson's disease. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:27 p.m.